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| Title: | Quinazoline derivatives, methods for the synthesis thereof and pharmaceutical preparations |
| Applicant: | F. Hoffman-La Roche & Co AG, Basel (Switzerland) |
| Representatives: | F. Lederer, Dr. R.F. Meyer, Patent Attorneys, 8000 Munich |
| Inventors | Chodnekar, Madhukar Subraya, Dr., Seltisberg; Kaiser, Ado, Dr., Lausen (Switzerland) |

[Rubber stamp
Patent Attorneys
Dr. Franz Lederer
Dr. Reiner F. Meyer, Engineer
8000 Munich 80
Lucile-Grahn Str. 22

July 20, 1978

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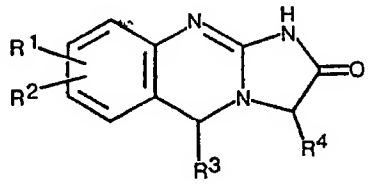
F. Hoffmann-La Roche & Co. Aktiengesellschaft, Basel/Switzerland

# QUINAZOLINE DERIVATIVES, METHODS FOR THE SYNTHESIS THEREOF AND PHARMACEUTICAL PREPARATIONS

The present invention relates to new tricyclic compounds, namely imidazo-quinazolines of the Formula




I

in which $R^1$ and $R^2$ represents hydrogen, a lower molecular weight alkyl, hydroxy, an alkoxy of lower molecular weight, a hydroxy alkyl of lower molecular weight, an alkoxyalkyl of lower molecular weight, halogen, phenyl, phenoxy, amino, an alkylamino of lower molecular weight or a dialkylamino of lower molecular weight, and $R^1$ and $R^2$ on adjacent carbon atoms also jointly represent methylene dioxy, $R^3$ represents hydrogen, an alkyl of lower molecular weight or phenyl, and $R^4$ represents a lower molecular weight alkyl, a hydroxyalkyl of lower molecular weight, an alkoxyalkyl of lower molecular weight, an arylalkyl of lower molecular weight or aryl, the tautomers thereof and the salts of such compounds.

The expression "lower molecular weight", used here, preferably refers to groups with 1 to 6 and especially with 1 to 4 carbon atoms. Alkyl groups may be linear or branched. Methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl are examples of alkyl groups. Aryl refers particularly to phenyl or to phenyl substituted by halogen, lower molecular weight alkyl, hydroxy and/or to phenyl-substituted by lower molecular weight alkoxy.

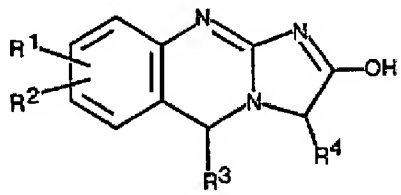
The compounds of Formula 1 preferably are present in the D form. Compounds of Formula I, in which $R^1$ and $R^2$ represent hydrogen, $R^2$ represents halogen in the 6 on 7 position or a lower molecular weight alkyl in the 6 position, particularly 6-chloro, 7-bromo or 6-methyl and $R^4$ represents lower molecular weight alkyl, particularly, methyl, are furthermore preferred.

Particularly preferred are
D-6-chloro-1,5-dihydro-2-methyl-imidazo[2,1-b]quinazoline-2(3H)-one,
D-1,5-dihydro-3,6-dimethyl-imidazo[2,1-b]quinazoline-2(3H)-one,
D-7-bromo-1,5-dihydro=3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one
and the salts thereof.

Examples of compounds of Formula 1 are
L-6-chloro-1,5-dihydro-2-3-hydroxymethyl-imidazo[2,1-b]quinazoline-2(3H)-one,
L-6-chloro-1,5-dihydro-3-phenyl-imidazo[2,1-b]quinazoline-2(3H)-one,
L-6-chloro-1,5-dihydro-3-isobutyl--imidazo[2,1-b]quinazoline-2(3H)-one,
L-3-benzyl-6-chloro-1,5-dihydro-imidazo[2,1-b]quinazoline-2(3H)-one
and the salts thereof.

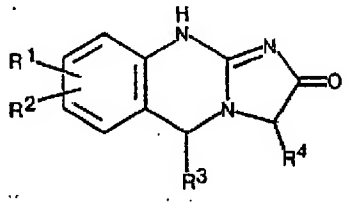
The invention furthermore relates to a method for the synthesis of the compounds named and to the production of pharmaceutical preparations based on the compounds named.

The compounds of Formula I may be present in various tautomeric forms. The invention is therefore not limited to compounds of the Formula I shown above and, instead, also comprises the tautomers, such as those of Formula




Ia

and



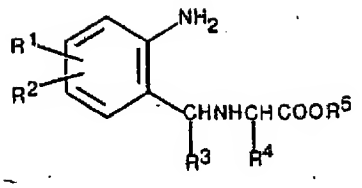

Ib

The compounds of Formula I and the tautomers thereof, such as Ia and Ib, furthermore may be present in the form of racemates or in an optically active form, all of these forms being a subject matter of the invention.

Examples of physiologically tolerated salts are mineral acid salts, such as hydrochlorides, hydrobromide, sulfates and phosphates; salts of organic sulfonic acids, such as alkyl sulfates, and aryl sulfonates and salts of carboxylic acids, such as succinates, citrates, tartrates and maleates.

According to the invention, the compounds of Formula I and the tautomers thereof can be synthesized owing to the fact that

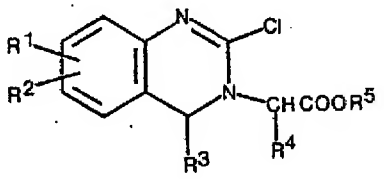
a) a compound of the Formula



II

in which $R^1$ to $R^4$ have the meanings given above and
$R^5$ represents a lower molecular weight alkyl, is reacted with bromocyan, or

b) a compound of the Formula



III

in which $R^1$ to $R^5$ have the meanings given above,
is treated with ammonia.

The reaction of a compound of Formula II with bromocyan advisably is carried out with heating in a solvent, such as a lower molecular weight alcohol, for example, ethanol. The reaction of a compound of Formula III with ammonia advisably is carried out with heating in a solvent, such as a lower molecular weight alcohol, for example, ethanol, and water.

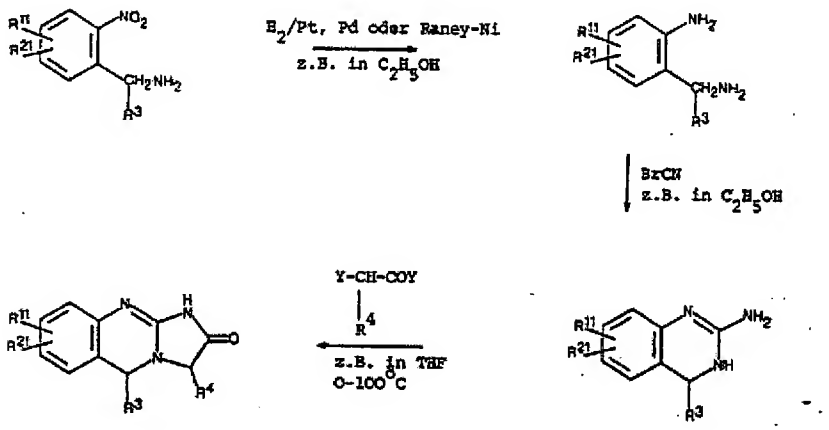
A compound of Formula I, in which $R^1$ and/or $R^2$ is hydrogen, can be halogenated by known methods. For example, an acetic acid solution of a compound, which is not substituted in positions 6, 7, 8 and 9 positions, can be reacted with bromine to form a 7-bromo compound.

The compounds of Formula I, in which $R^1$ and $R^2$ are different from an optionally alkylated amino group, can be synthesized according to the various

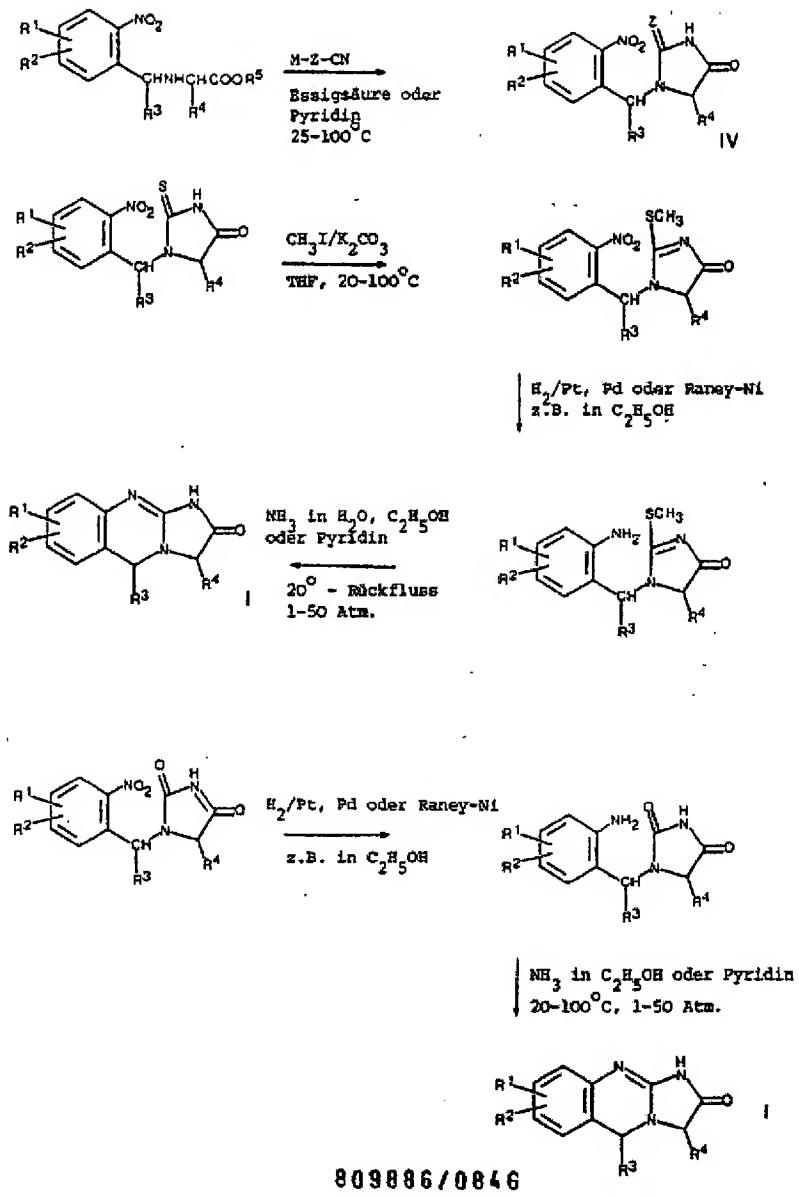
methods given in equation I below, in which Y represents chlorine or bromine, $R^{11}$ and $R^{21}$ have the same meanings as $R^1$ and $R^2$ with the exception of optionally alkylated amino and $R^3$ and $R^4$ have the above meanings.

The compounds of Formula I furthermore can be synthesized according to Equation II given below, in which Z represents oxygen or sulfur, M ammonium, potassium or sodium and the remaining symbols have the above meaning.

Equation I



Equation II

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Key for above Equations:

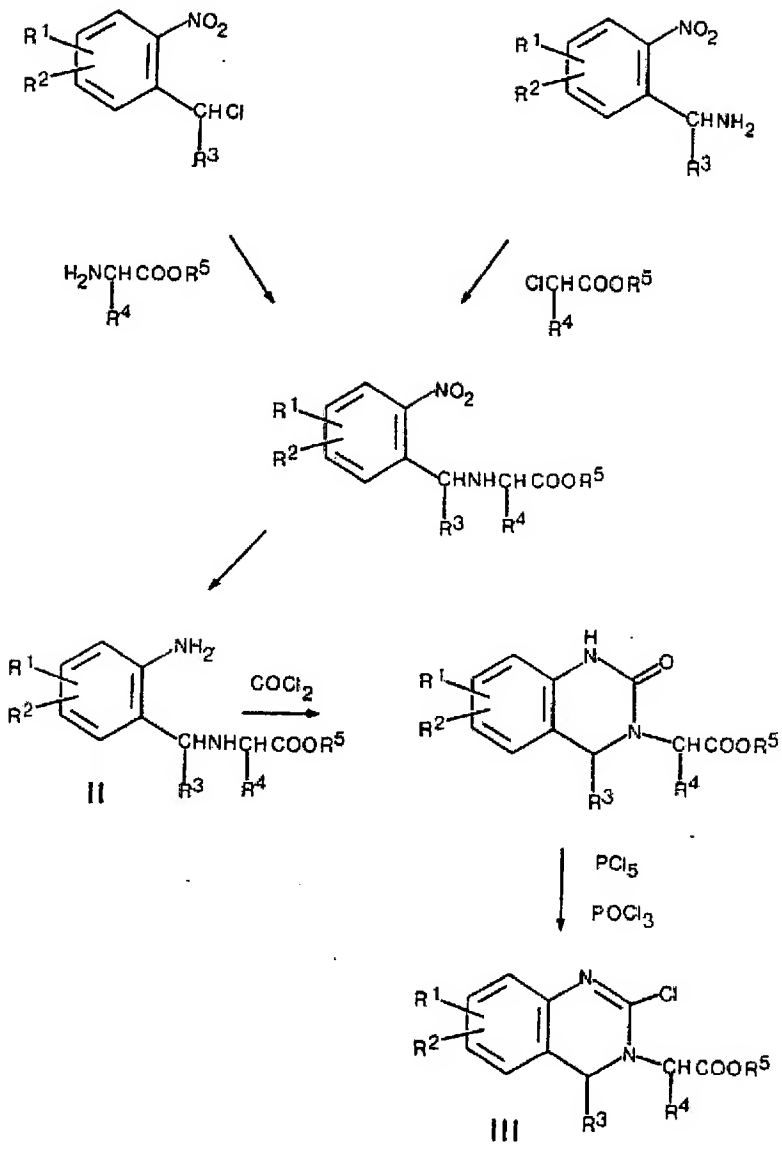
| | |
|---|---|
| Oder | Or |
| z.B. | For example |
| Essigsäure oder Pyridin | Acetic acid or pyridine |

Rückfluss Reflux

The compounds of Formula II are new and, as such, also are an object of the present invention.

The starting materials of Formulas II and III can be synthesized according to Equation III given below, wherein X represents halogen and the remaining symbols have the above meanings, or in analogy to the methods given in the Examples.

Equation III



The compounds of Formula I, the tautomers thereof and the physiologically tolerated salts of such compounds are to be used as medicinal drugs. They inhibit, for example, the aggregation of blood platelets and can therefore be used to prevent thromboses. In addition, they affect the circulation. Because of their positive inotropic effect, they can be used, for example, for the treatment and prophylaxis of heart failure and cardiac insufficiency without significant tachycardia.

The compounds of Formula I and the tautomers thereof can be used as medicinal drugs, for example, in the form of pharmaceutical preparations, in which they or the salts thereof are contained in an admixture with a pharmaceutical, organic or inorganic, inert carrier material, suitable for enteral, percutaneous or parenteral administration, such as water, gelatin, gum arabic, lactose, starch, magnesium stearate, talcum, vegetable oils, polyalkylene glycols, Vaseline, etc.. The pharmaceutical preparations may be present in solid form, for example, as tablets, sugar-coated pills, suppositories, capsules, in semi-solid form, for example, as ointments, or in liquid form, for example, as solutions, suspensions or emulsions. Optionally, they are sterilized and/or contain auxiliary materials, such as preservatives, stabilizers, wetting agents or emulsifiers, salts for changing the osmotic pressure or buffers. They may also contain other therapeutically valuable materials. Preferably, the compounds are administered orally. For adults, a daily oral dose of 0.05 to 30 mg/kg and a parenteral dose of 0.05 to 10 mg/kg come into consideration.

The aggregation-inhibiting activity was verified by the aggregometer method of Born (Nature 194, 927 (1962)) and Michal and Born (Nature 231, 220 (1971)). The maximum aggregation rate was taken as experimental parameter and the effective concentration ($EC_{50}$) determined from the dose-activity curves.

Human plasma was obtained from venous blood, mixed with citrate (10.6 mM), by centrifugation. Plasma (0.18 mL) was mixed with 10 μL of an

aqueous suspension of the test compound and incubated for 10 minute at 37°C, whereupon the aggregation was initiated by the addition of 10 μL of collagen fibril suspension.

Rabbit plasma was obtained by centrifuging arterial blood, mixed with citrate (9 mM). Plasma (1 mL) was mixed with 10 μL of test solution and incubated for 1 minute at 37°C, whereupon 8 μL of collagen fibril suspension or 10 μL of adenosine diphosphate (ADP) in $10^{-4}$ M sodium chloride solution were added. Plasma, incubated with dimethyl sulfoxide, served as control.

The results are given in Table I below.

The positive inotropic effect was measured on conscious sheepdogs after oral administration of the test substances. For this purpose, the animals are equipped with an implanted pressure telemetry system, the pressure detecting element being fixed in the left ventricle. The left ventricular pressure is transmitted from the animal over the implanted radio transmitter and received over a suitable antenna and receiver system, demodulated and amplified. The maximum pressure increase rate ($dLVP/dt_{max}$), which is regarded as the contractility parameter, is calculated by differentiating the rising leg of the left ventricular pressure (LVP). At the same time, the heart rate is recorded over a cardiotachograph. The percentage change (Δ%) of $dLVP/dt_{max}$ and the duration of action in minutes are given under inotropy. The percentage changes in the heart rate (Δ%) after the administration of the test substance and the duration of action in minutes are given under tachycardia. The results are reproduced in Table II below.

Table I

Collagen-induced and ADP-induced blood platelet aggregation

| Compound | Rabbit plasma | | Human plasma |
|---|---|---|---|
| | Collagen EC 50 μM | ADP EC 50 μM | Collagen EC 50 μM |
| D-1,5-dihydro-3,9-dimethyl-imidazo[2,1-b] quinazoline-one hydrochloride | 3.0 | 32 | 26 |
| L-1,5-dihydro-3,9-dimethyl-imidazo[2,1-b] quinazoline-one hydrochloride | 18 | 60 | 49 |
| D-1,5-dihydro-3,7-dimethyl-imidazo[2,1-b] quinazoline-one hydrochloride | 3.1 | 19 | 3.4 |
| L-1,5-dihydro-3,7-dimethyl-imidazo[2,1-b] quinazoline-one hydrochloride | 22 | 77 | 33 |
| D-1,5-dihydro-3,6-dimethyl-imidazo[2,1-b] quinazoline-one hydrochloride | 0.19 | 2.2 | 2.3 |
| L-1,5-dihydro-3,6-dimethyl-imidazo[2,1-b] quinazoline-one hydrochloride | 0.93 | 11 | 6.2 |
| L-1,5-dihydro-3-hydroxy-methyl-6-methyl-imidazo[2,1-b] quinazoline-one hydrochloride | - | - | 14 |

Table II

| Compound | Dose mg/kg | Inotropy | | Heart Rate | |
|---|---|---|---|---|---|
| | | Δ% | Min | Δ% | Min |
| D-6-chloro-1,5-dihydro-3-methyl-imidazo[2,1-b] quinazoline-one hydrochloride | 5 | 93 | 145 | 28 | 115 |
| D-1,5-dihydro-3,6-dimethyl-imidazo[2,1-b] quinazoline-one hydrochloride | 10 | 82 | 440 | 63 | 480 |
| L-1,5-dihydro-3,9-dimethyl-imidazo[2,1-b] quinazoline-one hydrochloride | 10 | 43 | 120 | 16 | 100 |

the following examples explain the invention. The temperatures are given in °C.

Example 1

A solution of 5.3 g bromocyan in 10 mL of ethanol was added at room temperature and with stirring to a solution of 11.8 g of N-(2-amino-3-methylbenzyl)-L-alanine ethyl ester. The reaction mixture was refluxed for 1 hour and then evaporated to dryness under a reduced pressure. The residue was mixed with 100 mL of water and made alkaline by the addition of 3N ammonium hydroxide with stirring. The mixture was then stirred for a further 30 minutes and extracted three times with 100 mL of methylene chloride. The organic extracts where washed twice with 150 mL of water, dried over sodium sulfate and evaporated. The residue was recrystallized from ethanol and yielded L-1,5-dihydro-3,9-dimethyl imidazo[2,1-b] quinazoline-one, having a missing point of 259° to 261°C and an $[\alpha]_D$ of +15.5° (c = 1% in methanol).

By recrystallizing the base, so obtained, from 1N hydrochloric acid and acetonitrile (3 : 1), the hydrochloride, having a melting point of 271° - 275°C (dec.) was obtained.

The staring material was prepared in the following manner:

A solution of 120 mL of triethylamine in 200 mL of absolute ethanol was added dropwise to a solution of 91.8 g of L-alanine ethyl ester hydrochloride in 300 mL of absolute ethanol. The reaction mixture was heated to 60°C, a clear solution being formed. A solution of 55.5 g of 3-(chloromethyl)-2-nitrotoluene in 300 mL of absolute ethanol was added dropwise to this solution over a period of 1 hour. Subsequently, the temperature was increased to 80°, the reaction mixture was stirred

overnight at this temperature and then evaporated to dryness under a reduced pressure. The residue was dissolved in 600 mL of water. The solution was extracted three times with methylene chloride and the extracts were washed with water and then with saturated sodium chloride solution, dried and evaporated. The crude product, so obtained, was purified by chromatography on silica gel with methylene chloride / 5% methanol as solvent. N-(3-methyl-2-nitrobenzyl)-L-alanine ethyl ester was obtained as a yellow oil, $[\alpha]_D$ -36° (c= 1% in methanol).

A solution of 26.6 g of N-(3-methyl-2-nitrobenzyl)-L-alanine ethyl ester in 100 mL of absolute ethanol wars hydrogenated in the presence of 2 g of 10% Pd/C. Over a period of 5 hours, 6.7 L of hydrogen being taken up. At the end of the hydrogenation, the catalyst was filtered off and the filtrate was evaporated to dryness. N-(2-amino-3-methylbenzyl)-L-alanine ethyl ester was obtained as a yellow oil, $[\alpha]_D$ - 52.6 ° (c= 1% in methanol .

The following compounds were synthesized analogously:

from 3-(chloromethyl)-2-nitrotoluene and D-alanine ethyl ester hydrochloride, the N-(3-methyl-2-nitrobenzyl)-D-alanine ethyl ester, yellow oil, $[\alpha]_D$ 31.4 ° (c= 1% in methanol ;

from $\alpha^3$-chloro-4-nitro-m-xylene and L-alanine ethyl ester hydrochloride, the N-(5-methyl-2-nitrobenzyl)-L-alanine ethyl ester, red oil, $[\alpha]_D$ - 12.6 ° (c= 1% in methanol);

from $\alpha^3$-chloro-4-nitro-m-xylene and D-alanine ethyl ester hydrochloride, the N-(5-methyl-2-nitrobenzyl)-D-alanine ethyl ester, red oil, $[\alpha]_D$ + 11.4° (c= 1% in methanol);

from $\alpha^2$-chloro-3-nitro-o-xylene and L-alanine ethyl ester hydrochloride, the N-(2-methyl-6-nitrobenzyl)-L-alanine ethyl ester, red oil, $[\alpha]_D$ + 35.8° (c= 1% in methanol);

from $\alpha^2$-chloro-3-nitro-o-xylene and D-alanine ethyl ester hydrochloride, the N-(2-methyl-6-nitrobenzyl)-D-alanine ethyl ester, red oil, $[\alpha]_D$ - 34° (c= 1% in methanol);

from $\alpha^2$-chloro-3-nitro-o-xylene and L-serine ethyl ester hydrochloride, the N-(2-methyl-6-nitrobenzyl)-L-serine ethyl ester, red oil, $n_D^{24}$ = 1.5474;

from $\alpha^2$-chloro-3-nitro-o-xylene and D-α-phenylglycine ethyl ester hydrochloride, the N-(2-methyl-6-nitrobenzyl)-D-α- phenylglycine ethyl ester, red oil, $n_D^{24}$ = 1.5261;

from 2-nitrobenzyl chloride and L-alanine ethyl ester hydrochloride, the 2-nitrobenzyl-L-alanine ethyl ester, dark red oil, $[\alpha]_D$ - 5.4 ° (c= 1% in ethanol);

from 2-nitrobenzyl chloride and D-alanine ethyl ester hydrochloride, the 2-nitrobenzyl-D-alanine ethyl ester, red oil, $[\alpha]_D$ + 5.4 ° (c= 1% in ethanol);

from N-3-methyl-2-nitrobenzyl-D-alanine ethyl ester, the N-(2-amino-3-methylbenzyl)-D-alanine ethyl ester, light yellow oil, $[\alpha]_D$ + 51° (c= 1% in methanol);

from N-(5-methyl-2-nitrobenzyl)-L-alanine ethyl ester, the N-(2-amino-5-methylbenzyl)-L-alanine ethyl ester, $[\alpha]_D$ - 45° (c= 1% in methanol);

from N-(5-methyl-2-nitrobenzyl)-D-alanine ethyl ester, the N-(2-amino-5-methylbenzyl)-D-alanine ethyl ester, red oil $[\alpha]_D$ + 34.2° (c= 1% in methanol);

from N-(2-methyl-6-nitrobenzyl)-L-alanine ethyl ester, the N-(2-amino-6-methylbenzyl)-L-alanine ethyl ester, yellow oil, $[\alpha]_D$ - 34.7° (c= 1% in methanol);

from N-(2-methyl-6-nitrobenzyl)-D-alanine ethyl ester, the N-(2-amino-6-methylbenzyl)-D-alanine ethyl ester, reddish oil, $[\alpha]_D$ + 36.8° (c= 1% in methanol);

from N-(2-methyl-6-nitrobenzyl)-L-serine ethyl ester, the N-(2-amino-6-methylbenzyl)-L-serine ethyl ester, red oil, $n_D^{24}$ = 1.5468;

from N-(2-methyl-6-nitrobenzyl)-D-α-phenylglycine ethyl ester, the N-(2-amino-6-methylbenzyl)- D-α-phenylglycine ethyl ester, yellow oil, $n_D^{24} = 1.5665$;

from (2-nitrobenzyl)-L-alanine ethyl ester, the 2-amino-benzyl-L-alanine ethyl ester, red oil, $[\alpha]_D$ -55.1° (c= 1% in ethanol);

from (2-nitrobenzyl)-D-alanine ethyl ester, the 2-amino-benzyl-D-alanine ethyl ester, dark red oil, $[\alpha]_D$ + 57.2° (c= 1% in ethanol).

Example 2

As in Example 1, D-1,5-dihydro-3,9-dimethylimidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from N-(2-amino-3-methylbenzyl)-D-alanine ethyl ester; it had a melting point of 270° to 275°C (dec.). The free base melts at 262° to 265°C.

Example 3

As in Example 1, L-1,5-dihydro-2,7-dimethyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from N-(2-amino-5-methylbenzyl)-L-alanine ethyl ester; it had a melting point of 173° to 176°C. The free base melts with decomposition above 300°C.

Example 4

As in Example 1, D-1,5-dihydro-3,7-dimethyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from N-(2-amino-5-methylbenzyl)-D-alanine ethyl ester as light yellow crystals with a melting point of 173° to 176°C (dec.). The free base melts with decomposition at 310° - 314C°.

Example 5

As in Example 1, L-1,5-dihydro-3,6-dimethyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from N-(2-amino- 6-methylbenzyl)-L-alanine ethyl ester as colorless crystals with a melting point of 285° to 288°C (dec.). The free base melts with decomposition above 340°C.

Example 6

As in Example 1, D-1,5-dihydro-3,6-dimethyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from N-(2-amino- 6-methylbenzyl)-D-alanine ethyl ester as light yellow crystals with a melting point of 287° to 290°C (dec.). The free base melts above 340°C.

Example 7

As in Example 1, L-1,5-dihydro-3-hydroxymethyl-6-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from N-(2-amino-6-methylbenzyl)-L-serine ethyl ester as yellow crystals with a melting point of 320° to 325°C (dec.).

Example 8

As in Example 1, D-1,5-dihydro-3-phenyl-6-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from N-(2-amino-6-methylbenzyl)-D-α-phenylglycine ethyl ester as light yellow crystal with a melting point of about 320°C (dec.).

Example 9

As in Example 1, L-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from 2-amino-benzyl-L-alanine ethyl ester as brown crystals with a melting point of 223° to 226°C. The free base melts with decomposition at 300° - 305°C.

Example 10

As in Example 1, D-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained from 2-amino-benzyl-D-alanine ethyl ester as yellow crystals with a melting point of 225° to 227°C (dec.). The free base melts with decomposition at about 300°C.

Example 11

A solution of 5 g of bromocyan in 20 mL of ethanol was added dropwise with stirring to a solution of 11.9 g of N-(2-amino-6-chlorobenzyl)-L-alanine ethyl ester in 20 mL of ethanol. The reaction mixture was then refluxed for 1 hour and evaporated to dryness. The residue was mixed with 150 mL of water and made alkaline with 3N ammonium hydroxide while stirring. After stirring for 30 minutes, the precipitate was filtered off and recrystallized from 1N HCl and acetonitrile, 9.1 g (68% of the theoretical amount) of L-6-chloro-1,5-hydro-3-methyl--imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride being obtained as yellow crystals with a melting point of 260° - 263°C and an $[\alpha]_D$ of + 34.2° (DMSO).

D-6-chloro-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride was obtained similarly from N-(2-amino-6-chlorobenzyl)-D-

alanine ethyl ester; melting point 263° - 266°C, $[\alpha]_D$ - 23.9 ° (DMSO), melting point of the free base 275° - 280°C.

The starting material can be synthesized as follows:

A mixture of 25 mL of triethylamine in 60 mL of ethanol was added dropwise to 18.24 g of L-alanine ethyl ester hydrochloride in 60 mL of ethanol and heated to 80°C. A solution of 15 g of α-bromo-2-chloro-6-nitrotoluene in 60 mL of ethanol was added dropwise to the resulting solution at this temperature. The mixture was stirred overnight at 80°C and then evaporated to dryness. The residue was mixed with 150 mL of deionized water and extracted twice with methylene chloride. The methylene chloride extracts where washed with water, dried and evaporated. The duct so obtained was purified by chromatography on silica gel with methylene chloride / 5% methanol, 15.75 g (91% of the theoretical amount) of N-(2-chloro-6-nitrobenzyl-L-alanine ethyl ester with an $n_D^{20}$ of 1.5267 being obtained.

N-(2-chloro-6-nitrobenzyl)-D-alanine ethyl ester was obtained similarly from D-alanine ethyl ester and α-bromo-2-chloro-6-nitrotoluene, $n_D^{20}$: 1.5247.

A solution of 14.3 g of N-(2-chloro-6-nitrobenzyl)-L-alanine ethyl ester in 50 mL of absolute ethanol was hydrogenated in the presence of 1 g of Raney nickel. At the end of the hydrogenation, the catalyst was filtered off and the filtrate was evaporated to dryness, 12.6 g (99% of the theoretical amount) of N-(2-amino-6-chlorobenzyl)-L-alanine ethyl ester, with an $n_D^{20}$ of 1.5430, was obtained.

N-(2-amino-6-chlorobenzyl)-D-alanine ethyl ester with an $n_D^{23}$ of 1.5405 was obtained similarly by the hydrogenation of N-(2-chloro-6-nitrobenzyl)-D-alanine ethyl ester.

Example 12

The following compounds were synthesized by a method analogous to that of Example 11:

D-6,7-dichloro-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, with a melting point above 280°C,

L-6,7-dichloro-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, with a melting point above 290°C,

D-7-bromo-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, with a melting point of 268° - 280°C,

L-7-bromo-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, with a melting point of 280° - 284°C (dec.),

L-6-chloro-7-methoxy--1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, with a melting point above 280°C.

Example 13

The following compounds were synthesized by a method analogous to that of Example 11:

from N-(2-chloro-6-nitrobenzyl)-3-phenyl-D-alanine ethyl ester, $[\alpha]_D$ - 21.2° (c = 1% in ethanol) over N-(2-amino-6-chlorobenzyl)-3-phenyl-D-alanine ethyl ester, $[\alpha]_D$ + 40.7° (c = 1% in ethanol), the D-3-benzyl-6-chloro-1,5-dihydroimidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, M.P.: 260° - 265°C (dec.); M.P. of the base: 270° - 275°C (dec.),

from N-(2-chloro-6-nitrobenzyl)-D-leucine ethyl ester over N-(2-amino-6-chlorobenzyl)-D-leucine ethyl ester, $[\alpha]_D$ + 8.5° (c = 1% in ethanol), the D-

6-chloro-1,5-dihydro-3-isobutylimidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, M.P.: 290° - 293°C; M.P. of the base: 280° - 285°C ,

from N-(2-chloro-6-nitrobenzyl)-D-serine ethyl ester, $[\alpha]_D$ 2.7° (c = 1% in ethanol), over N-2-(amino-6-chlorobenzyl)-D-serine ethyl ester, M.P. 73° - 75°C, $[\alpha]_D$ + 65.5° (c = 1% in ethanol), the D-6-chloro-3-hydroxymethyl-1,5-dihydro-limidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, M.P. of the base: above 300°C (dec.),

from D-N-(2-chloro-6-nitrobenzyl)-2-phenylglycine ethyl ester, $[\alpha]_D$ - 21° (c = 1% in ethanol), over D-N-(2-amino-6-chlorobenzyl)-2-phenylglycine ethyl ester, $[\alpha]_D$ - 4.5° (c = 1% in ethanol), the D-6-chloro-3-phenyl-1,5-dihydro-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride, M.P.: above 300°C (dec.), melting point of the base: 260° - 265°C (decd.).

Example 14

A mixture of 6 g of ethyl-D-2,5-.chloro-α-methyl-3-(4H)-quinazoline acetate, 20 mL of absolute ethanol and 25 mL of 5% alcoholic ammonia was heated overnight at 110°C in a sealed tube. The sealed tube was cooled in an ice bath and opened. The resulting crystalline paste was filtered off with suction and washed with cold ethanol. The crystals obtained were dissolved in 1N HCl and filtered. The filtrate was evaporated to dryness and the residue was recrystallized from 1N HCL and acetonitrile as D-6-chloro-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride (4.3 g, 74% of the theoretical yield) M.P.: 275°C - 278°C.

The starting material can be synthesized in the following manner:

A mixture of 25 mL of triethylamine in 60 mL of ethanol was added clockwise to a mixture of 18.24 g of D- alanine ethyl ester hydrochloride in 60 mL of ethanol and heated to 80°C. The resulting solution was added dropwise at this

temperature to a solution of 15 g of 2-chloro-6-nitro-benzyl bromide in 60 mL of ethanol. The mixture was stirred overnight at 80°C and then evaporated to dryness. The residue was mixed with 150 mL of de-ionized water and extracted twice with 100 mL of methylene chloride. The methylene chloride extracts were washed with water, dried over sodium sulfate and evaporated. The product, so obtained, was purified by chromatography on silica gel with methylene chloride / 5% methanol. N-(2-chloro-6-nitrobenzyl)-D-alanine ethyl ester, $n_D^{25}$: 1.5247, $[\alpha]_D$ - 6.9° (c = 1% ethanol) was obtained in a yield of 16 g (93% of the theoretical).

A solution of 14.3 g of N-(2-chloro-6-nitrobenzyl)-D-alanine ethyl ester in 50 mL of ethanol was hydrogenated in the presence of 1 g of Raney nickel. Over a period of 2 hours, 3.35 L of hydrogen were taken up. The catalyst was then filtered off and the filtrate was evaporated to dryness, 12.6 g (99% of the theoretical) of N-(2-amino-6-chlorobenzyl)-D-alanine ethyl ester, with $n_D^{23}$ 1.5405, $[\alpha]_D$ + 55.8° (c = 1% ethanol), being obtained.

N,N"-carbonyl diimidazole (52 g) was added in portions, with stirring and under nitrogen to a solution of 71.75 g of N-(2-amino-6-chlorobenzyl)-D-alanine ethyl ester in 400 mL of dry tetrahydrofuran. The mixture was stirred for two hours and refluxed 18 hours and evaporated to dryness and the residue was extracted with 1500 mL of methylene chloride, the organic phase washed twice with 400 mL of 1N HCl and then with 400 mL of water, dried and evaporated. The oil, so obtained, was purified by chromatography on silica gel with methylene chloride / 5% methanol. Yield: 75 g (99% of the theoretical) of ethyl-D-5-chloro-1,4-dihydro-α-methyl-2-oxo-3(2H)-quinazoline acetate with an $[\alpha]_D$ - 40.8 ° (c = 1% in ethanol)

Ethyl-D-5-chloro-1,4-dihydro-α-methyl-2-oxo-3(2H)-quinazoline acetate (50.9 g was dissolved in 135 mL of phosphoroxy chloride and heated for three hours with stirring at 110°C. The reaction mixture was then cooled and evaporated to dryness and the residue was dissolved in 250 mL of chloroform, the

solution diluted with 300 mL of ice water and adjusted to a pH of 7-8 by the dropwise addition of 40% sodium hydroxide solution. The chloroform phase was removed, dried and evaporated. The product was purified by chromatography on silica gel with methylene chloride / 5% methanol. Yield: 37.4 g (70% of the theoretical) of ethyl-D-2,5-dichloro-α-methyl-3(4H)-quinazoline acetate with an $n_D^{22}$ of 1.5775.

Example 15

Bromine (1.5 mL) is added dropwise to a solution of 5 g of D-1,5-dihydro-3-methylimidazo-(2,1-b]quinazoline-2(3H)-one in 80 mL of glacial acetic acid. The mixture is stirred for 90 minutes at room temperature, diluted with 100 mL of water and evaporated to 30 mL, diluted once again with 100 mL of water, made alkaline with 3N ammonium hydroxide solution, washed and filtered. The precipitated product is washed with water and recrystallized from 100 mL of 2N HCl, 3.9 g (56% of the theoretical) of D-7-bromo-1,5-dihydro-3-methyl-imidazo(2,1-b]quinazoline-2(3H)-one hydrochloride with a melting point of 268° - 270°C being obtained.

Example 16

In a manner similar to that of Example 15, 4.7 g of L-1,5-dihydro-3-methylimidazo-(2,1-b]quinazoline-2(3H)-one are brominated to form 4.2 g (64%) of L-7-bromo-1,5-dihydro-3-methylimidazo-(2,1-b]quinazoline-2(3H)-one hydrochloride, having a melting point of 280° - 284°C. (dec.)

Example 17

Tablets of the following composition are prepared in the usual manner:

| | |
|---|---|
| D-6-chloro-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride | 184.6 mg |
| Lactose | 15.0 mg |
| Corn starch | 37.9 mg |
| Water-soluble polyvinylpyrrolidone | 10.0 mg |
| Magnesium stearate | 2.5 mg |
| Total weight per tablet | 250.0 mg |

Example 18

Gelatin capsules of the following composition were prepared in the usual manner:

| | |
|---|---|
| D-6-chloro-1,5-dihydro-3-methylimidazo[2,1-b]quinazoline-2(3H)-one hydrochloride | 200.0 mg |
| Water soluble polyvinylpyrrolidone | 2.0 mg |
| Corn starch | 43.9 mg |
| Talcum | 4.5 mg |
| Magnesium stearate | 0.5 mg |
| Total weight per tablet | 250.0 mg |

Example 19

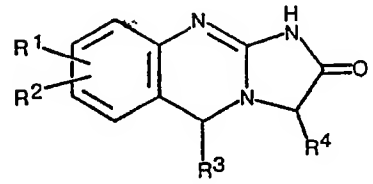
An injection solution of the following composition was prepared in the usual manner:

| | |
|---|---|
| D-6-chloro-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one hydrochloride | 114.16 mg |

| | |
|---|---|
| Glycerin formal | 2.4 mg |
| Water | 4.0 mL |

## Claims

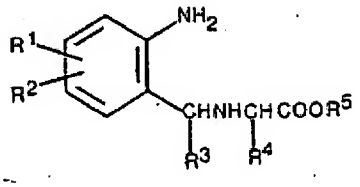
1. A method for the synthesis of compounds of Formula



I

in which $R^1$ and $R^2$ represents hydrogen, a lower molecular weight alkyl, hydroxy, an alkoxy of lower molecular weight, a hydroxy alkyl of lower molecular weight, an alkoxyalkyl of lower molecular weight, halogen, phenyl, phenoxy, amino, an alkylamino of lower molecular weight or a dialkylamino of lower molecular weight, and $R^1$ and $R^2$ on adjacent carbon atoms also jointly represent methylenedioxy, $R^3$ represents hydrogen, an alkyl of lower molecular weight or phenyl, and $R^4$ represents a lower molecular weight alkyl, a hydroxyalkyl of lower molecular weight, an alkoxyalkyl of lower molecular weight, an arylalkyl of lower molecular weight or aryl, the tautomers thereof and the salts of such compounds, characterized in that

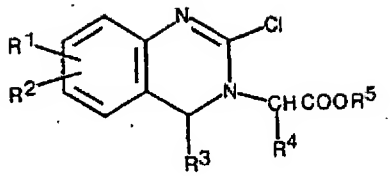
a) a compound of the Formula



II

in which $R^1$ to $R^4$ have the meanings given above and
$R^5$ represents a lower molecular weight alkyl, is reacted with bromocyan, or

b) a compound of the Formula



III

in which $R^1$ to $R^5$ have the meanings given above,
is treated with ammonia.

2. The method of claim 1, characterized in that the starting point is a compound of Formula II or III in the D form.

3. The method of claims 1 or 2, characterized in that the starting point is a compound of Formula II or III, in which $R^1$ and $R^2$ represent hydrogen, $R^2$ represents halogen in the 6 or 7 position or a lower molecular weight alkyl in the 6 position and $R^4$ represents a lower molecular weight alkyl.

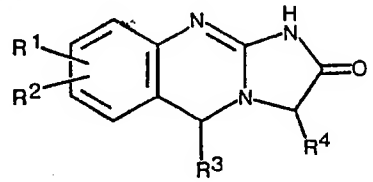
4. The method of claims 1, 2 or 3, characterized in that the starting point is a compound of Formula II or III, wherein $R^1$ and $R^3$ represent hydrogen, $R^2$ represents 6-chloro, 7-bromo or 6-methyl and $R^4$ represents methyl.

5. The method of one of the claims 1 to 4 for the synthesis of D- 6-chloro-1,5-dihydro-3-methylimidazo[2,1-b]quinazoline-2(3H)-one and salts thereof.

6. Method for the synthesis of pharmaceutical preparations, characterized in that a compound of Formula I according to the definition in claim 1, a tautomer thereof or a physiologically tolerated salt of such a compound is mixed as effective component with nontoxic, inert, solid and liquid carriers and/or excipients, suitable for therapeutic administration and customary in such preparations.

7. Pharmaceutical preparation, characterized by a content of a compound of Formula I according to the definition in claim 1, a tautormer thereof or a physiologically tolerated salt of such a compound.

8. Compounds of Formula




I

in which $R^1$ and $R^2$ represents hydrogen, a lower molecular weight alkyl, hydroxy, an alkoxy of lower molecular weight, a hydroxy alkyl of lower molecular weight, an alkoxyalkyl of lower molecular weight, halogen, phenyl, phenoxy, amino, an alkylamino of lower molecular weight or a dialkylamino of lower molecular weight, and $R^1$ and $R^2$ on adjacent carbon atoms also jointly represent methylene dioxy, $R^3$ represents hydrogen, an alkyl of lower molecular weight or phenyl, and $R^4$ represents a lower molecular weight alkyl, a hydroxyalkyl of lower molecular weight, an alkoxyalkyl of lower molecular weight, an arylalkyl of lower molecular weight or aryl, the tautomers thereof and the salts of such compounds.

9. The compounds of claim 8 in the D form.

10. The compounds of claims 8 or 9, wherein $R^1$ and $R^2$ represent hydrogen, $R^2$ represents halogen in the 6 or 7 position or a lower molecular weight alkyl in the 6 position and $R^4$ represents a lower molecular weight alkyl.

11. Compounds of claims 8, 9 or 10, wherein $R^1$ and $R^3$ represent hydrogen, $R^2$ represents chlorine in the 6 position, bromine in the 7 position or methyl in the 6 position and $R^4$ represents methyl.

12. D-6-chloro-1,5-dihydro-3-methyl-imidazo[2,1-b]quinazoline-2(3H)-one and salts thereof.